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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 10/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/743,731	SMIT, JOHN	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication..
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-6 and 9-12 are pending in the application.

[2] Applicant's amendment to the claims, filed September 07, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's arguments filed September 07, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

[5] In view of the amendment to the claims, the objections to claim 1 as set forth at items [6] and [7] of the Office action mailed April 01, 2004, are withdrawn.

Claim Rejections - 35 USC § 112, Second Paragraph

[6] Claim(s) 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 (claims 10-12 dependent therefrom) recites the limitation "the S-layer protein of said *Caulobacter crescentus*" in line 6. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112, First Paragraph

[7] In view of applicants' deletion of the limitation at issue, the new matter rejection of claims 1-6 under 35 U.S.C. 112, first paragraph, as set forth at item [9] of the Office action mailed April 01, 2004, is withdrawn.

[8] The written description rejection of claims 1-6 and newly added claims 9-12 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth at item [10] of the Office action mailed April 01, 2004, and for the reasons stated below.

RESPONSE TO ARGUMENTS: Applicants argue the specification discloses five examples of the recited genus of *C. crescentus* S-layer proteins that include a secretion signal, *i.e.,* amino acids 622-1026, 690-1026, 784-1026, 892-1026, and 907-1026 of SEQ ID NO:5. Applicants argue the examiner has provided no evidence to support an assertion that S-layer protein fragments are widely variant such that the fragments of amino acids 622-1026, 690-1026, 784-1026, 892-1026, and 907-1026 of SEQ ID NO:5 are not representative of the genus of recited fragments. Applicants argue the claims are not directed to identification of *Caulobacter* S-layer protein fragments that include a secretion signal, but are directed to methods of cleaving an insoluble fusion protein. Applicants argue that, based on the disclosure and state of the art at the time of

the invention, the cited fragments as disclosed in the specification represent the entire genus of recited fragments. Applicants' argument is not found persuasive.

In response to applicants' argument that the disclosed fragments of ., amino acids 622-1026, 690-1026, 784-1026, 892-1026, and 907-1026 of SEQ ID NO:5 represent the entire genus of recited fragments, the examiner acknowledges the disclosure of the cited fragments of SEQ ID NO:5. However, it is noted that these fragments are all generated from a single representative species, *i.e.*, the amino acid sequence of SEQ ID NO:5 and, as stated in a previous Office action, the single representative species of SEQ ID NO:5, including fragments thereof, fails to represent the entire genus of recited *C. crescentus* S-layer protein fragments. It should be noted that the claims are not limited to the disclosed fragments of SEQ ID NO:5 and, in accordance with MPEP 2111, broadly encompass any sequence of amino acids that one of skill in the art would consider to be a *C. crescentus* S-layer protein fragment that includes a secretion signal. In this regard it should also be noted that the specification fails to provide any characteristics of a *C. crescentus* S-layer protein fragment that includes a secretion signal such that a skilled artisan would be able to distinguish such a protein fragment from any other protein fragment comprising a secretion signal. As the claims are not limited to any particular structure and the examiner knows of no correlation between the structure of a *C. crescentus* S-layer protein and the pseudo-functional recitation of "*C. crescentus* S-layer protein fragment which includes a secretion signal," the claims encompass a vast number of polypeptides. As such, the species encompassed

by the genus are widely variant with respect to their structures. In this case, the single representative species of SEQ ID NO:5 and fragments thereof fail to represent the entire genus of recited fragments.

In response to applicants' argument that the claims are not directed to identification of *Caulobacter* S-layer protein fragments that include a secretion signal, the examiner acknowledges the claims are drawn to methods and not to the *Caulobacter* S-layer protein fragments. However, it is noted that the recited genus of *Caulobacter* S-layer protein fragments is an essential or critical element of the claimed invention and must be described in accordance with MPEP 2163. In this case, it is the examiner's position that the single representative species of SEQ ID NO:5, including fragments thereof, is not representative of the genus of *Caulobacter* S-layer protein fragments. At least for the reasons stated above, the specification fails to satisfy the requirements for adequate written description under 35 U.S.C. 112, first paragraph.

[9] The scope of enablement rejection of claims 1-6 and newly added claims 9-12 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth at item [11] of the Office action mailed April 01, 2004, and for the reasons stated below.

RESPONSE TO ARGUMENTS: Applicants argue that methods for identifying the portion of the C-terminus of a particular *Caulobacter* S-layer protein are known and routine to those skilled in the art, citing WO 97/34000 as evidence thereof. Applicants argue that by using routine techniques and without undue experimentation, a skilled artisan can make the full scope of recited *C.*

crescentus S-layer protein fragments. Applicants' argument is not found persuasive.

First, as stated above, the specification fails to provide any characteristics of a *C. crescentus* S-layer protein fragment that includes a secretion signal such that a skilled artisan would be able to distinguish such a protein fragment from any other protein fragment comprising a secretion signal. Thus, in accordance with MPEP 2111, the scope of proteins that are considered to be a "first component" encompasses a vast number of proteins that comprise a secretion signal. Even assuming *arguendo* a skilled artisan could distinguish a *C. crescentus* S-layer protein fragments comprising a secretion signal from any other protein, the full scope of recited *C. crescentus* S-layer protein fragments is not enabled by the specification.

Further, regarding the merits of applicants' argument, the examiner maintains the position that undue experimentation is required for a skilled artisan to make the full scope of recited *C. crescentus* S-layer protein fragments as broadly encompassed by the claims at least for the reasons of record. The examiner acknowledges that methods of identifying fragments of a given protein having a particular function, *e.g.*, active site of an enzyme, region(s) of protein-protein interaction, signal sequence, are known. However, in this case, the claims are not limited to a particular structure of *C. crescentus* S-layer protein, and thus, in accordance with MPEP 2111, broadly encompass mutants and variants of a *C. crescentus* S-layer protein. The specification fails to identify those amino acids of SEQ ID NO:5 – or any other *C. crescentus* S-layer protein –

that are required or not required for proper localization/function/solubility such that one of skill could alter the sequence of SEQ ID NO:5 – or any other *C. crescentus* S-layer protein – with an expectation of obtaining a polypeptide having the desired utility. Without such guidance, the effects of mutating even a single amino acid in a given protein are highly unpredictable. In this case, it is not routine to screen for all *C. crescentus* S-layer protein fragments, including mutants and variants thereof, that have the desired utility as broadly encompassed by the claims.

Claim Rejections - 35 USC § 103

[10] The rejection of claims 1-6 and newly added claims 9-12 under 35 U.S.C. 103(a) as being unpatentable over Smit et al. in view of Nomellini et al., Ausubel et al., and Better is maintained for the reasons of record and the reasons stated below.

RESPONSE TO ARGUMENTS: Applicants argue there is no suggestion in the prior art to include an aspartate-proline cleavage site in a *C. crescentus* S-layer fusion protein and one would not be motivated to practice the claimed methods. Applicants argue that even if the prior art had made such a suggestion, one of ordinary skill in the art would not have had a reasonable expectation of success for successfully practicing the claimed methods because: 1) Nomellini et al. do not teach a fragment of an *C. crescentus* S-layer protein that "simply includes a secretion signal" would be acid insoluble and 2) the cited references

are silent as to whether an insoluble protein could be cleaved at an Asp-Pro bond. Applicants' argument is not found persuasive.

The examiner acknowledges that no single reference teaches a *C. crescentus* S-layer protein fusion protein comprising an Asp-Pro cleavage site. If one of the cited references had disclosed such teachings, the rejection likely would have been made under 35 U.S.C. 102. It is the *combination* of references that renders the claimed methods obvious – not one single reference or a subcombination thereof. In the instant case, the claims are not limited to any particular sequence of a *C. crescentus* S-layer protein that "simply includes" a secretion signal. Thus, in accordance with MPEP 2111, the acid-insoluble protein as taught by Nomellini et al. is encompassed by a "*Caulobacter crescentus* S-layer protein fragment which includes a secretion signal" or " a fragment of the S-layer protein of said *Caulobacter crescentus*, said fragment including a secretion signal" as recited in the claims. As such, contrary to applicants' assertions, in view of the *combination* of the references, one of ordinary skill in the art would have had motivation and a reasonable expectation of success for practicing the claimed methods.

Conclusion

[11] Status of the claims:

- Claims 1-6 and 9-12 are pending.
- Claims 1-6 and 9-12 are rejected.
- No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

10-25-04

David J. Steadman
Primary Examiner
Art Unit 1652